Appl. No. : **09/776,232**
Filed : **February 02, 2001**

REMARKS

Claims 38-59, 60 and 61 are pending in the present application. Non-elected Claims 52-59 have been cancelled without prejudice. Claims 38, 45, 60, and 61 have been amended. New Claim 62 has been added. Accordingly, Applicants respectfully submit that the application is now in condition for allowance.

Support for the amendments can be found throughout the specification and in the claims as originally filed, for example, on page 6, lines 19-21; page 59, line 32 to page 60, line 1; page 60, lines 29-32; page 63, lines 26-28; page 67, lines 18-20; page 69, lines 25-31; and the examples. Accordingly, no new matter has been added to the application by entering this amendment.

Pursuant to the USPTO Revised Format for Amendments, the amendments to the claims are shown by ~~strikethrough~~ for deleted matter and underlining for added matter. No accompanying "clean" version has been supplied.

Elections

Applicants affirm the provisional election made without traverse to prosecute the invention of group I, claims 38-51.

IDS

Applicants submitted an IDS, Paper No. 3, without copies of the references as the references were submitted in the parent application 09/380,534. The Office Action requests that Applicants resubmit the references. Accordingly, copies of the references will follow shortly by courier or hand-delivery.

Rejection Under 35 U.S.C. § 102

Claims 38, 40, 41, 43, 45, 48, 49, 50 and 51 were rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Felgner *et al.*, U.S. Patent No. 5,589,466 (Felgner). Specifically, the Office Action asserts that Felgner at col. 5, line 39 through col. 8, line 10 "discloses a method of inducing and maintaining a CTL response in a mammal including delivering an antigen in the form of a nucleic acid encoding the antigen directly to the lymphatic system (i.e., spleen, 7:1-4)."

Appl. No. : 09/776,232
Filed : February 02, 2001

Claims 38, 40, 41, 43, 45, 46, 48, 49, 50 and 51 were rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Carson *et al.*, U.S. Patent No. 5,679,647 (Carson). Specifically, the Office Action asserts that Carson "discloses delivering a nucleic acid encoding an antigen to antigen presenting cells (veiled cells of afferent lymphatics and interdigitating cells of lymphoid organs, 5:56-59)."

Finally, Claims 38, 40, 41, 43, 45, 46, 48, 49, 50 and 51 were rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Kubo *et al.*, U.S. Patent No. 6,037,135 (Kubo). Specifically, the Office Action asserts that Kubo "discloses delivering a nucleic acid encoding an antigen to lymphoid tissue via liposomes. (15:45-59)."

Applicants respectfully disagree with the Office Action, and submit that the pending claims are allowable over these references.

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991) (emphasis added).

Claims 38 and 45 have been amended to include the feature of delivering the antigen directly to a lymph node or lymph vessel. Support for this amendment can be found throughout the specification and in the claims as originally filed, for example, on page 6, lines 19-21; page 59, line 32 to page 60, line 1; page 60, lines 29-32; page 63, lines 26-28; page 67, lines 18-20; page 69, lines 25-31; and the examples. Applicants have discovered unexpectedly that delivery directly to the lymph node can be about 10-fold more efficient than direct delivery to the spleen. Applicants respectfully submit that this feature is missing from each of the cited references as discussed below. Claims 40, 41, and 43 depend from Claim 38, and Claims 48-57 depend from Claim 45. Accordingly, Applicants' claims are all directed to delivering the antigen directly to a lymph node or lymph vessel, which is not taught in Felgner, Carson, or Kubo.

Appl. No. : **09/776,232**
Filed : **February 02, 2001**

Felgner does not teach direct delivery of antigen to the lymph nodes or lymph vessels.

Felgner discloses a method for delivering a pharmaceutical or immunogenic polypeptide to the interior of a cell of a vertebrate *in vivo*, wherein the method may be used to elicit an immune response. Felgner discloses that "[i]n preferred embodiments, the polynucleotide is introduced into muscle tissue; in other embodiments the polynucleotide is incorporated into the tissues of skin, brain, lung, liver, spleen or blood." Felgner, at col. 7, lines 1-4.

Felgner does not disclose delivering the antigen directly to the lymph node or lymph vessels. Accordingly, Felgner does not teach every claim feature of the claims of the instant application.

Because Felgner does not teach every feature of the independent Claims 38 and 45, Claims 38, 40, 41, 43, 45, 48, 49, 50 and 51 are novel under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request that this rejection be withdrawn.

Carson does not teach direct delivery of antigen to the lymph nodes or lymph vessels.

Carson teaches the administration of naked polynucleotides to the immunological periphery where the polynucleotides will then be expressed intracellularly in immature antigen presenting cells (APCs). Immature pAPCs traverse the immunological periphery, acquire antigen, then travel to secondary lymphoid organs, such as the spleen and lymph nodes, where they mature and present processed antigens to T-cells. This is evidenced in Carson's discussion of the preferred embodiment, in which the target tissue is the skin or mucosa, with the APCs "serv[ing] as vehicles to deliver the naked polynucelotide to lymphatic organs and to mucosal tissues other than those at the point of entry." Carson, at col. 7, lines 62-65; col. 8, lines 1-5. Thus, Carson teaches indirect delivery to lymphatic organs and to mucosal tissues. Carson does not teach or suggest direct delivery to a lymph node or lymph vessel.

Because Carson does not disclose delivering the antigen directly to the lymph node or lymph vessels, it does not teach every feature of the claims of the instant application.

Because Carson does not teach every feature of independent Claims 38 and 45, Claims 38, 40, 41, 43, 45, 48, 49, 50 and 51 are novel under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request that this rejection be withdrawn.

Appl. No. : 09/776,232
Filed : February 02, 2001

Kubo does not teach direct delivery of antigen to the lymph nodes or lymph vessels.

Kubo discloses compositions comprising immunogenic peptides which can be administered to a patient via conventional administration routes to elicit a cytotoxic T lymphocyte (CTL) response. In preferred embodiments, the compositions are administered intravenously, subcutaneously, intradermally, or intramuscularly. Kubo, at col. 15, lines 17-19. Thus, Kubo teaches delivery of the immunogenic peptides to the immunological periphery. Kubo teaches that the compositions may be "administered via liposomes, which target the peptides to a particular cells [sic] tissue, such as lymphoid tissue." Kubo, at col. 15, lines 45-47. Thus, the liposomes act as vehicles to deliver antigen to lymphoid cells. Kubo explicitly acknowledges this fact, at col. 15, lines 51-59, stating that the peptide to be delivered can be in conjunction with a molecule that binds to a receptor prevalent among lymphoid cells. Thus, the liposomes may be "directed to the site of lymphoid cells, where the liposomes then deliver the selected therapeutic/immunogenic peptide compositions." *Id.* Accordingly, Kubo teaches indirect delivery of antigen to lymphoid tissues.

Kubo does not disclose delivering the antigen directly to the lymph node or lymph vessels. Accordingly, Kubo does not teach every feature of the claims of the instant application.

Because Kubo does not teach every feature of independent Claims 38 and 45, Claims 38, 40, 41, 43, 45, 48, 49, 50 and 51 are novel under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request that this rejection be withdrawn.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 102.

Rejection Under 35 U.S.C. § 103

Claims 38-42, 45-47, 49-51, 60 and 61 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Vitiello *et al.*, U.S. Patent No. 6,419,931 (Vitiello) in view of Kundig, *Science* 268:1343-47 (1995) (Kundig). In addition, Claims 38-51 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Bot *et al.*, U.S. Patent No. 6,204,250 (Bot) in view of Kundig.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be

a reasonable expectation of success found in the prior art. Third, the prior art must reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Claims 38-42, 45-47, 49-51, 60 and 61 are patentable over Vitiello in view of Kundig.

The Office Action asserts that Vitiello discloses a method of inducing and maintaining a CTL response in a mammal. The Office Action notes that Vitiello does not disclose administering the antigen directly to the lymphatic system. However, the Office Action asserts that Kundig teaches the step of delivering antigen directly to the lymphatic system, and argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Kundig in the method of Vitiello in order to efficiently elicit a CTL response.

Applicants respectfully disagree with the rejections, and submit that the pending claims are allowable over these references because there is no suggestion to combine these references and there is no reasonable expectation of success in practicing the claimed invention using the disclosures of Vitiello and Kundig. In addition, there is no recognized need in Vitiello that would motivate the combination of these references. Furthermore, the methods of Vitiello teach away from practicing the claimed invention. Finally, neither Vitiello nor Kundig nor the combination of the two references teaches or suggests all the claim features of the instant application.

The first criterion of a *prima facie* case of obviousness requires that there be a suggestion or motivation to modify the references or to combine reference teachings to achieve the claimed invention. "[I]t is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016 (CCPA 1972); M.P.E.P. 2143.01. Applicants submit that neither Vitiello nor Kundig provides suggestion or motivation to modify or combine the reference teachings to achieve the claimed invention.

Vitiello teaches inducing or stimulating a CTL response using a composition comprising a combination of a peptide constituting a CTL epitope, a peptide constituting a helper T cell (HTL) epitope, wherein one of the peptides is lipidated and/or the composition further comprises an adjuvant, using conventional routes of administration. The use of an HTL epitope containing

a lipidated peptide and/or a conventional adjuvant is required in the method of Vitiello as no CTL response was obtained when the HTL epitope was omitted. Vitiello, at col. 29, lines 47-49.

Vitiello achieved a CTL response using the specific immunogenic compositions and conventional boosting regimens and routes of administration (i.e. intravenously, subcutaneously, intradermally, or intramuscularly). Vitiello, at col. 15, lines 15-37, and ex. 11. Accordingly, Vitiello provides no recognized need to deliver antigens directly to the lymphatic system. Thus, Vitiello provides no suggestion or motivation to utilize direct delivery to the lymphatic system.

Kundig examined the role of professional antigen presenting cells (APCs) in achieving a CTL response. Kundig discloses that a CTL response can be induced without the use of professional APCs (pAPCs) through the use of cell-associated antigens. Specifically, Kundig discloses that "mice injected with fibroblasts expressing viral proteins developed strong antiviral CTL responses, without any involvement of professional APCs." Kundig, at 1343. Kundig further discloses that "fibroblasts induced T cell responses only when they reached the lymphoid organs." *Id.* Kundig concludes that "cells other than professional APCs can directly induce T-cells." *Id.* Namely, Kundig concludes that fibroblasts can function as immunogenic APCs if located in the lymphoid organs. *Id.* at 1346.

Fibroblasts are not pAPCs. CTL responses are typically induced when fragments of cell-free protein antigens are presented in association with Class I Major Histocompatibility Complex (MHC) molecules on the surface of specialized cells termed pAPC. Immature pAPCs traverse the immunological periphery, acquire antigen, then travel to secondary lymphoid organs, such as the spleen and lymph nodes, where they mature and present processed antigens to T-cells. Thus, antigen acquisition and presentation typically takes place within the lymphatic system.

Kundig discloses only the delivery of cell-associated antigens, namely, fibroblasts expressing viral proteins. Thus, Kundig teaches the use of non-pAPC to present antigens, wherein antigen acquisition and presentation takes place entirely outside and independent of the lymphatic system.

Kundig is completely silent as to the delivery of cell-free antigens directly to the lymphatic system, wherein the antigens are then processed and presented by pAPC within the lymphatic system. Furthermore, the methods of Vitiello and Kundig are not interchangeable because mature pAPC, which make up a considerable proportion of the pAPC found in lymph nodes, are much less efficient at taking up and presenting antigens. Thus, one of skill in the art

would not expect an advantage in delivering cell-free antigens directly to the lymphatic system. Accordingly, the use of fibroblasts acting directly in antigen presentation, as disclosed by Kundig, does not suggest any advantage in delivering cell-free peptide antigens directly to the lymphatic system. Thus, there is no suggestion or motivation to combine the teachings of Vitiello and Kundig.

Furthermore, Vitiello teaches away from the combination of these references. Vitiello teaches the administration of cell-free peptide antigens with the obligate inclusion of adjuvant or lipidation of the peptide antigens. Administration of many adjuvants directly to the lymphatic system would be expected to provoke a pathologically strong response, such as a severe inflammatory response, that those of skill in the art would seek to avoid. Furthermore, many adjuvants would destroy the cellular integrity that was essential to the success of Kundig. Kundig, at page 1344. Accordingly, because the specific form and formulation of antigen is crucial to the success of the methods of each of the cited references, the differences in the form and formulation of antigen taught by Vitiello and the form and formulations of antigen taught by Kundig teach away from the combination of these references. In other words, the teachings of these references are incompatible and therefore a person of ordinary skill in the art would not be motivated to combine them. Since there is neither any suggestion nor any motivation to combine the teachings of Vitiello and Kundig, Vitiello in view of Kundig fails to provide sufficient teachings to render the claimed invention obvious.

The second criterion of a *prima facie* case of obviousness requires that there be a reasonable expectation of success derived from the cited reference in practicing the claimed invention. *In re Merck & Co., Inc.*, 800 F2d. 1091, 231 USPQ 375 (Fed. Cir 1986); M.P.E.P. 2143.02. At least some degree of predictability is required with respect to a reasonable expectation of success. Predictability is provided, in part, by providing a detailed description. Vitiello and Kundig fail to provide one of skill in the art with a reasonable expectation of success to practice the claimed invention, and therefore, do not render the claimed invention obvious.

The Office Action asserts that Kundig teaches the step of delivering antigen directly to the lymphatic system, and argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Kundig in the method of Vitiello in order to efficiently elicit a CTL response. However, as discussed above, Kundig provides no discussion concerning the delivery of cell-free antigens directly to the lymphatic system, wherein

the antigens are then processed and presented by pAPC within the lymphatic system. Moreover, the methods of Vitiello and Kundig are not interchangeable because mature pAPC, which make up a considerable proportion of the pAPC found in lymph nodes, are much less efficient at taking up and presenting antigens.

Furthermore, Vitiello teaches away from the practice of the claimed invention, because including adjuvants as taught by Vitiello would be expected to provoke a very undesirable response if delivered directly to the lymphatic system. Thus, one of skill in the art would have no reasonable expectation of success in practicing the claimed invention based on the disclosures of Vitiello and Kundig.

Given the lack of a reasonable expectation of success in practicing the claimed invention in view of the disclosures of Vitiello and Kundig and in view of the fact the references teach away from the claimed invention, the second criterion for establishing a *prima facie* case of obviousness has not been met.

The third criterion requires that the cited art teach or suggest all the limitations of the claims. "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382 (CCPA 1970); M.P.E.P. 2143.03. A comparison of the pending claims with the subject matter disclosed in Vitiello and the subject matter disclosed in Kundig shows that these references do not teach or suggest all of the limitations of the claims. As discussed above, neither Vitiello nor Kundig nor the combination of the two references teaches or suggests the direct delivery of cell-free antigen to the lymphatic system.

Accordingly, the combination of Vitiello in view of Kundig fails to satisfy any of the three criteria for establishing a *prima facie* case because the cited references, alone or in combination, fail to describe or teach the claims of the instant application. Therefore, the cited references do not provide sufficient teachings to render the claimed invention obvious. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Finally, the unexpected result, as discussed above, in which direct delivery to a lymph node generates a response that is about 10-fold more efficient than delivery to the spleen, is also evidence of the non-obviousness of the claims. *See, e.g., In re Chupp*, 816 F.2d 643,646 (Fed. Cir. 1987) (unexpected increased effectiveness); *Ex parte A*, 17 U.S.P.Q. 2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity); M.P.E.P. § 716.02(a).

Claims 38-51 are patentable over Bot in view of Kundig.

The Office Action asserts that Bot discloses a method of inducing and maintaining a CTL response in a mammal including delivering antigen in the form of a nucleic acid encoding antigen. The Office Action notes that Bot does not disclose administering the antigen directly to the lymphatic system. However, the Office Action argues that Kundig teaches the step of delivering antigen directly to the lymphatic system, and it would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Kundig in the method of Bot in order to efficiently elicit a CTL response.

Applicants respectfully disagree with the rejections, and submit that the pending claims are allowable over these references because there is no suggestion to combine these references and there is no reasonable expectation of success in practicing the claimed invention using the disclosures of Bot and Kundig. Furthermore, there is no recognized need in Bot that would motivate the combination of these references. Finally, neither Bot nor Kundig nor the combination of the two references teaches or suggests all the claim features of the instant application.

The first criterion of *a prima facie* case of obviousness requires a suggestion or motivation to modify the reference or to combine reference teachings to achieve the claimed invention. Applicants submit that neither Bot nor Kundig provides suggestion or motivation to modify or combine the reference teachings to achieve the claimed invention.

Bot teaches prophylactic immunization of infants in which an initial immunization using nucleic acid antigen is followed some time later by a booster immunization with live virus. Bot, at col. 8, lines 27-29. Thus, Bot teaches the administration of nucleic acids via conventional routes of administration, whereby the nucleic acid is taken up and the antigen expressed by local immature pAPC, which later migrate to the lymph nodes, mature, and present the antigen.

Bot achieved a CTL response using the specific immunogenic compositions and intramuscular administration. Bot, at col. 11, lines 33-64. Accordingly, Bot provides no recognized need to deliver antigens directly to the lymphatic system. Thus, Bot provides no suggestion or motivation to utilize direct delivery to the lymphatic system.

As discussed above, Kundig teaches the administration of cell-associated antigens directly into the spleen. Kundig is completely silent as to the delivery of cell-free antigens

directly to the lymphatic system, wherein the antigens are then processed and presented by pAPC within the lymphatic system. Because cell-free antigens are presented by pAPC, the use of fibroblasts acting directly in antigen presentation, as disclosed by Kundig, does not suggest an advantage in delivering cell-free antigens directly to the lymphatic system.

The forms of antigen and methods of administration used in Kundig and the forms of antigen and methods of administration used in Bot would not be viewed by one of ordinary skill in the art as interchangeable. This is because mature pAPC, which make up a considerable proportion of the pAPC found in lymph nodes, are much less efficient at taking up and presenting antigens. Furthermore, the differences between the forms of antigen and methods of administration teach away from the combination of these references. Accordingly, there is no suggestion or motivation to combine the teachings of Bot and Kundig.

The second criterion of a *prima facie* case of obviousness requires a reasonable expectation of success derived from the cited reference in practicing the claimed invention. *In re Merck & Co., Inc.*, 800 F2d. 1091, 231 USPQ 375 (Fed. Cir 1986); M.P.E.P. 2143.02. Both Bot and Kundig fail to provide one of skill in the art with a reasonable expectation of success in making the combination that is alleged to render the claims obvious.

The Office Action asserts that Kundig teaches the step of delivering antigen directly to the lymphatic system, and argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Bot in the method of Kundig in order to efficiently elicit a CTL response. However, as discussed above, Kundig provides no discussion concerning the delivery of cell-free antigens directly to the lymphatic system, wherein the antigens are then processed and presented by pAPC within the lymphatic system. Moreover, because mature pAPC make up a considerable proportion of the pAPC found in the lymph nodes, and because nucleic acid antigens are presented by pAPC, one of ordinary skill in the art would have no reasonable expectation of success in delivering nucleic acid antigens directly to the lymphatic system. Thus, one of skill in the art would have no reasonable expectation of success in practicing the claimed invention based on the disclosures of the Bot and Kundig.

The third criterion requires that the cited art teach or suggest all the limitations of the claims. "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382 (CCPA 1970); M.P.E.P. 2143.03. A comparison of the pending claims with the subject matter disclosed in Bot and the subject matter

disclosed in Kundig shows that these references do not teach or suggest all of the limitations of the claims. As discussed above, neither Bot nor Kundig nor the combination of the two references teaches or suggests the direct delivery of cell-free antigen to the lymphatic system.

Accordingly, the combination of Bot in view of Kundig fails to satisfy any of the three criteria for establishing a *prima facie* case because the cited references, alone or in combination, fail to describe or teach the claims of the instant application. Therefore, the cited references do not provide sufficient teachings to render the claimed invention obvious. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The claimed carrier for antigen in Claim 44 is not well known in the art.

The Office Action further asserts that the use of the claimed carrier for antigen in Claim 44 is well known in the art. In addition, the Office Action asserts that the use of a pump to deliver therapeutic liquid is notoriously well known in the art. Applicants assume the second assertion is directed to Claim 61 which relates to delivering a liquid comprising an antigen directly to the lymph node or lymph vessel of the mammal from a device external to the mammal. The Office Action provides no factual support for these assertions.

Applicants respectfully disagree with the Office Action that the claimed carrier for antigen in Claim 44 is well known in the art. Applicants also respectfully disagree with the Office Action that the use of an external device to deliver a liquid comprising an antigen directly to the lymph node or lymph vessels is notoriously well-known in the art. Applicants respectfully note that "[t]he examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." M.P.E.P. § 2142. Applicants further note that "[i]f the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." *Id.* Accordingly, Applicants respectfully request that this unsupported rejection be withdrawn.

For the foregoing reasons, the Office Action has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 38-42, 45-47, 49-51, 60 and 61 under 35 U.S.C. § 103 as being unpatentable over Vitiello in view of Kundig. Likewise, Applicants respectfully request withdrawal of the rejection of Claims 38-51 under 35 U.S.C. § 103 as being unpatentable over Bot in view of Kundig.

Appl. No. : **09/776,232**
Filed : **February 02, 2001**

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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